REMARKS

I. Status Summary

Claims 1, 6, and 8 are pending in the present U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the amendments to claim 1 presented in previously filed Amendment C added new matter.

Claims 1 and 6 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are unpatentable over Liu *et al.* (88 *J Pharmaceutical Sci* 1161-1168, 1999; hereinafter "Liu").

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Liu.

Claim 1 has been amended. Support for the amendment to claim 1 can be found throughout the specification as filed, including particularly in Figure 2A. Additional support can be found on page 5, lines 18-23; page 14, lines 5-8; and page 14, lines 21-24 of the instant specification. Thus, no new matter has been added by the amendment to claim 1.

Reconsideration of the application based on the application as amended and in light of the remarks set forth below is respectfully requested.

II. Response to the New Matter Rejection

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the amendments to claim 1 presented in previously filed Amendment C added new matter. According to the Patent Office, the recitation of 13 to 20 methylene groups is new matter in view of the disclosure in the specification of phospholipase C inhibitors having 9-20 alkyl groups.

Applicants respectfully disagree. Applicants respectfully submit that the instant rejection appears to be based on the assertion that the narrowed range of straight-chain alkyls from 9-20 methylene groups to 13-20 methylene groups

constitutes new matter. Applicants respectfully submit, however, that the specification as filed includes several instances wherein the number of methylene units in the alkyl chain is disclosed as being between 9 and 20, with each integer between 9 and 20 also being explicitly disclosed.

For example, applicants direct the Patent Office's attention to the description of Figure 2A presented on page 5 of the specification as filed. This description states that:

> Figure 2A is a structural formula, Formula 1, for the alkylphosphocholines prepared for structure activity relationships analysis in accordance with the present invention. Six alkylphosphocholines were synthesized or acquired that contained 10, 12, 14, 16, 18, or 20 methylene units in their alkyl chain, i.e. n=9, 11, 13, 15, 17 or 19. However, as shown in Fig. 2A, n can also be 8, 10, 12, 14, 16 or 18.

Specification at page 5, lines 18-23. Figure 2A has been reproduced below:

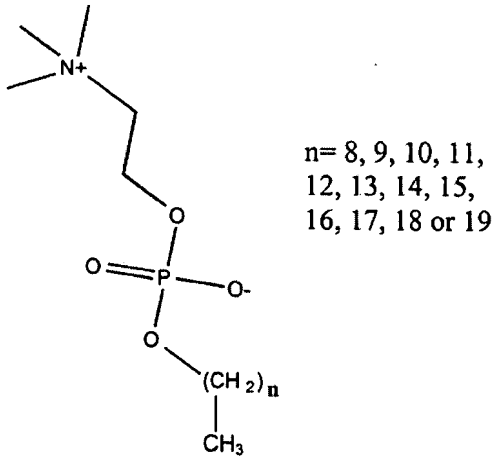


FIGURE 2A

As can be seen in Figure 2A, the subject matter of the present application relates in some embodiments to alkyl phosphocholines with a straight-chain alkyl of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 methylene units between the terminal methyl and the phosphate group, resulting in a total of 9-20 alkyl groups in the alkyl phosphocholines. Additionally, page 14, lines 5-8 of the instant specification state that "the alkylphosphocholine can further

comprise an alkyl chain of ten to twenty methylene groups, i.e. an alkyl chain of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 methylene groups". Page 14, lines 21-24 of the instant specification also state that "the alkylphosphocholine can further comprise an alkyl chain of ten to twenty methylene groups, i.e. an alkyl chain of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 methylene groups". And finally, page 18, lines 8-9 of the instant specification cites Figure 2A, and discloses that "analogs of C16 were synthesized that varied in chain length by 10 to 20 methylene units (Figure 2A, Formula 1)".

Accordingly, applicants respectfully submit that the specification as filed explicitly discloses alkyl chains of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 methylene groups, and thus explicitly discloses alkyl chains of 13, 14, 15, 16, 17, 18, 19, or 20 methylene groups. Thus, applicants respectfully submit that the instant new matter rejection is improper, and respectfully request that it be withdrawn at this time.

The Patent Office's attention is also directed to M.P.E.P. § 2163.05, Item III., which discusses Range Limitations and *In re Wertheim* (541 F.2d 257, 191 USPQ 90 (CCPA 1976)). In *Wertheim*, the Court of Customs and Patent Appeals held that while a disclosure of a range of "25%-60%" and specific examples of "36%" and "50%" did not support a new claim limitation to "at least 35%", it did indeed support a range of "between 35% and 60%". Thus, in *Wertheim*, a broad range with disclosure of specific intermediate data points was deemed to support a claim element from one of the intermediate data points to the top of the disclosed range. In the instant case, the disclosure recites a broad range (*i.e.*, 9-20 methylene units) and intermediate data points (*i.e.*, each integer value between 9 and 20), and thus supports the narrowed range. Accordingly, applicants respectfully submit that for this additional reason the instant rejection is improper.

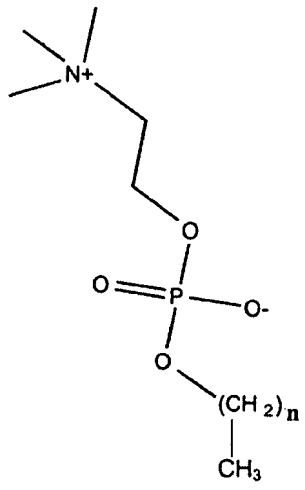
Furthermore, page 18, lines 8-9 of the instant specification cites Figure 2A, and discloses that "analogs of C16 were synthesized that varied in chain length by 10 to 20 methylene units (Figure 2A, Formula 1)". Figure 2A depicts straight-chain alkyls of 9-20 carbons, which are referred to in the instant

specification as 9-20 "methylene" units or groups. While it might be arguable that the term "methylene group" would ordinarily refer to a CH_2 group and thus would not include the terminal CH_3 group, applicants respectfully submit that they have employed the term to include both the CH_2 group and the terminal CH_3 group.

> To elaborate, the Brief Description of Figure 2A recites the following:
>
> Six alkylphosphocholines were synthesized or acquired that contained 10, 12, 14, 16, 18, or 20 methylene units in their alkyl chain, i.e. n=9, 11, 13, 15, 17 or 19. However, as shown in Fig. 2A, n can also be 8, 10, 12, 14, 16 or 18.

Specification at page 5, lines 20-23 (emphasis added). If **n** in Figure 2A equaling 9, 11, 13, 15, 17, or 19 corresponds to 10, 12, 14, 16, 18, or 20 methylene units, respectively, applicants respectfully submit that it is clear that the terminal CH_3 is being included as a "methylene unit" in the instant disclosure. Thus, for this additional reason applicants respectfully submit that the instant rejection is improper.

Nonetheless, in an effort to facilitate the prosecution of the instant claims, applicants have amended claim 1 to recite *inter alia* administering an effective amount of a phospholipase C inhibitor to a subject at a time in which enhanced paracellular permeability is desired, wherein the phospholipase C inhibitor comprises the following structure:



where n = 12-19. Applicants respectfully submit that the passages cited hereinabove fully support the amended claim language.

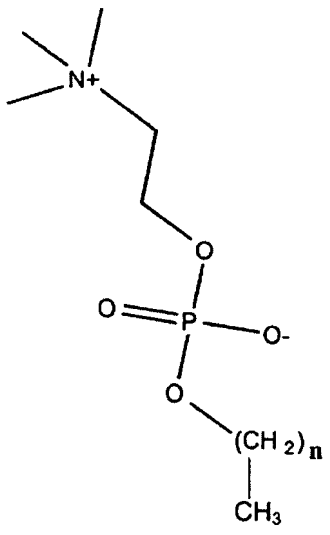
Accordingly, applicants respectfully submit that the rejection of claims 1, 6, and 8 under the first paragraph of 35 U.S.C. 112 has been addressed. Applicants respectfully request that the instant rejection be withdrawn, and further that the claims be allowed at this time.

III. Response to the Rejection under 35 U.S.C. § 102(b)

Claims 1 and 6 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Liu. According to the Patent Office, Liu discloses that dodecylphosphocholine (DPC) improves paracellular permeability across the intestinal epithelium.

After careful review of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, claim 1 has been amended to recite that the alkylphosphocholine has the following structure:



where n = 12-19. DPC has a structure that would define **n** as 11. As such, Liu does not disclose any alkylphosphocholines with the structure recited in claim 1,

and thus applicants respectfully submit that Liu does not teach each and every element of claim 1.

Accordingly, applicants respectfully submit that claim 1 has been distinguished over Liu. Claim 6 depends from claim 1, and thus is also believed to be distinguished over Liu. As a result, applicants respectfully request that the rejection of claims 1 and 6 under 35 U.S.C. § 102(b) be withdrawn, and the claims allowed at this time.

IV. Response to the Rejection under 35 U.S.C. § 103(a)

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu. According to the Patent Office, Liu teach that DPC can improve paracellular permeability of certain compounds across the intestinal epithelium.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following comments.

Initially, applicants respectfully submit that the Patent Office asserts in the instant Final Official Action that "PLC inhibition is of no moment primarily since PLC inhibition is not recited in [claim 1]. Claim 1 only recites the administration of a PLC inhibitor, of which DPC is as per the instant specification". (Final Official Action at page 6). Applicants respectfully submit, however, that this statement indicates that the Patent Office is approaching the analysis of the claims from an improper perspective and is attempting to "read out" the element from claim 1 that the method of enhancing paracellular permeability comprises *inter alia* administering a PLC inhibitor and enhancing paracellular permeability through the administering of the effective amount of the phospholipase C inhibitor. Applicants respectfully submit that a proper analysis under 35 U.S.C. § 103(a) must consider the claim as a whole, which the Patent Office's current approach appears not to do.

Continuing with the instant rejection, applicants respectfully submit that the disclosure of Liu does not suggest that alkylphosphocholines comprising the

structure set forth in claim 1 where n = 12-19 would also enhance paracellular permeability. Therefore, applicants respectfully submit that the disclosure of Liu provides no reasonable expectation to one of ordinary skill in the art that other alkylphosphocholines, particularly the alkylphosphocholines recited in claim 1, would have activity in enhancing paracellular permeability. Applicants respectfully submit that in the absence of a reasonable expectation of success, a *prima facie* case of obviousness can not be established.

And finally, even assuming *arguendo* that the Patent Office has established a *prima facie* case of obviousness of claim 1 over Liu, applicants respectfully submit that as set forth in M.P.E.P. § 2141.01, "[o]bjective evidence or secondary considerations such as unexpected results...are relevant to the issue of obviousness and must be considered in every case in which they are present" (emphases added). Applicants respectfully submit that the instant specification clearly discloses that the claimed alkylphosphocholines are superior to DPC, and further that the potency of these recited alkylphosphocholines represents a highly unexpected result.

To elaborate, applicants respectfully submit that the instant specification discloses that:

> [t]he potency of alkylphosphocholines, which corresponded to the concentration of alkylphosphocholines that decreased TEER by 50% (EC_{50}), varied markedly (Table 2). Interestingly, small variations in the alkyl chain produced significant ($p<0.05$) changes in the EC_{50} of these compounds. For example, C16 and C12 differ by four methylene units in their alkyl chain, but their respective EC_{50} values differ by approximately 25-fold.

Specification at page 30, lines 19-24 (emphasis added). Review of the data presented in Table 2 further indicates that despite the fact that DPC differs from the C14, C16, C18, and C20 compounds by only 2, 4, 6, or 8 methylene groups, respectively, these compounds are 17-fold, 25-fold, 12-fold, and 10-fold more potent than DPC, respectively. In fact, the instant specification discloses that "C10 and C12 are the least potent enhancers of paracellular permeability in this series" (*see* Specification at page 33, lines 13 and 14). As such, applicants

respectfully submit that the potency of the claimed alkylphosphocholines represents an unexpected result relative to that of DPC.

Applicants further respectfully submit that even if the Patent Office were to base the instant rejection on a contention of structural similarity between DPC and the alkylphosphocholines recited in claim 1, its asserted *prima facie* case would be rebutted by the significantly superior properties demonstrated for the latter over DPC (*see* M.P.E.P. § 2144.09, "a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties". *citing In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); emphasis added).

Summarily, applicants respectfully submit that the Liu reference does not support a *prima facie* case of obviousness of claims 1, 6, and 8 under 35 U.S.C. § 103(a), and even if a *prima facie* case were established, it would be rebutted by the unexpectedly superior properties of the claimed alkylphosphocholines. As such, applicants respectfully submit that claims 1, 6, and 8 have been distinguished over Liu, and further that these claims are in condition for allowance at this time. Applicants respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge deficiencies in payment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR & HUNT, P.A.

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